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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/216,609	12/21/98	HANSEN H	018733/0734

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EXAMINER	
HOLLERAN, A	
ART UNIT	**PAPER NUMBER**
1642	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/216,609	Applicant(s) HANSEN, HANS JOHN	
	Examiner Anne Holleran	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *8-13,15-22,27,28,30,33-35,42-44,47 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,14,23-26,29,31,32,36-41,45,46 and 49-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The amendment filed May 14, 2001 is acknowledged.

Claim 54 was canceled.

The elected species for beginning a search of the prior art are: enzyme: carboxylesterase; prodrug: CPT-11, target site: CEA antigen; therapeutic agent: camptothecin. Therefore, the following claims are withdrawn from consideration: 8-13, 15-22, 27, 28, 30, 42-44, 47 and 48. Claims 33-35 are also withdrawn from consideration because they read on methods where no prodrug is administered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

3. The rejection of claim 54 under 35 U.S.C. 102(b) as being anticipated by Bosslet et al (Bosslet, K. Cancer Research, 54: 2151-2159, 1994; IDS ref. "A29") is withdrawn in view of the cancellation of claim 54.

4. The rejections of claims 12, 14 and 15 under 35 U.S.C. 103(a) as being unpatentable over Sharma et al (Sharma, S.K. et al., Br. J. Cancer, 61: 659-662, 1990; IDS ref. "A28"), Blakey et al (Blakey, D.C. et al, Cancer Res. 56: 3287-3292, 1996), or Bagshawe et al (Bagshawe, K.D. et al., Br. J. Cancer, 58: 700-703, 1988; IDS ref. "A21") in view of Martinis et al (WO 83/03679,

published Oct. 27, 1983) are withdrawn because Martinis fails to teach bispecific antibodies that bind to enzymes.

5. The rejection of claims 7 and 45 under 35 U.S.C. 103(a) as being unpatentable over Potter et al (Potter, P.M., Cancer Research, 58(16): 3627-3632, 1998, August; abstract only) in view of either Bosslet, Sharma or Blakey, and further in view of Martinis et al is withdrawn because Martinis fails to teach bispecific antibodies that bind to enzymes.

6. The rejection of claim 22 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment to claim 22.

Claim Rejections Maintained:

7) The rejection of claim 23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for the reasons of record and for new grounds.

Applicant's arguments are not convincing and it is not clear from the passage in the specification pointed to and from the recitation of claim 23 that the second substance is present at the target site. Furthermore, claim 1 does not provide for a second substance. Therefore, claim 23 is indefinite because it improperly broadens the scope of claim 1.

8. The rejection of claims 1-6, 11, 12, 16-18, 20, 31-34, 36, 39, 42-44, 46 and 49-53 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of U.S. Patent 5,851,527 is maintained for the reasons of record. A terminal disclaimer was not found with the file.

Priority:

9. The priority of claims 1-53 has been further considered. The instant application claims priority, as a continuation-in-part, to copending application 08/445,110 (now U.S. Patent 5,851,527) filed May 19, 1995, which was a continuation of 07/182,623 (now abandoned), filed Apr. 18, 1988. The priority of new claims is assessed in view of written description requirement of 35 U.S.C. 112, 1st paragraph. Upon further consideration, it does not appear that as of the filing dates of either of the parent applications, that applicant was in possession of the full scope of the instantly claimed inventions. Therefore, for the purposes of comparing the claimed inventions with the prior art, the filing date of the instant application, Dec. 21, 1998, will be used.

Claims 1-53 contain subject matter that was not fully described in parent application 08/445,110. Claims 1-53 are drawn to methods comprising the use of, kits, or sterile, injectable preparations of multispecific targeting proteins or targeting protein-enzyme conjugate. Parent application 08/445,110 fails to describe the full scope of compounds encompassed by the phrase "multispecific targeting protein" or "targeting protein-enzyme conjugate". Parent application 08/445,110 confines its description to bispecific antibodies made by covalent conjugation of two antibodies or two antibody subfragments derived from papain digestion, and to bispecific

antibodies made by the polydoma technique. The phrase "multispecific targeting protein" broadens the scope of products described in the parent application and supported by the disclosure of the parent application. For example, "multispecific targeting protein" encompasses conjugates of single chain antibodies or fusion proteins, which are not described in the parent application, and "targeting protein enzyme-conjugate" encompasses fusion proteins, which are not described in the parent application.

New Grounds of Rejection:

10. Claims 24-27, 29, 30, 33-35, 40, 41 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 is indefinite because it appears to broaden the scope of claim 1. Claim 24 is drawn to a method where more than one substance is targeted whereas claim 1 recites targeting only one substance.

Claims 25-27, 29 and 30 are indefinite because they appear to broaden the scope of claim 1. Claims 25-27, 29 and 30 are drawn to methods where more than one enzyme is administered, whereas claim 1 recites a method where only one enzyme is administered.

Claim 33 is indefinite because it is drawn to a method where the targeting protein, the enzyme, or both, comprises a therapeutic agent such that step (c) results in the in situ formation of a targeting protein-enzyme conjugate comprising a therapeutic agent. However, claim 33 depends from claim 1 which requires the performance of step (e) (providing a prodrug

composition). Because claim 33 is a method where the therapeutic agent is already present by the action of step (c), it is not clear what the purpose of step (e) is.

Claims 40 and 41 are indefinite because the phrase "the lysine residues" lacks antecedent basis.

11. Claims 1, 2, 5-7, 14, 45, 46, 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iwasa (U.S. Patent 5,506,135, issued April 9, 1996; effective filing date Sep. 26, 1989) in view of either Bosslet et al (Bosslet, K. et al, Cancer Research, 54: 2151-2159, 1994; IDS ref. "A29"), or Blakey et al (Blakey, D.C. et al, Cancer Res. 56: 3287-3292, 1996), and further in view of Potter et al (Potter, P.M., Cancer Research, 58(16): 3627-3632, 1998, August; abstract only).

Claims 1, 2, 5-7, 14, 45, 46, 49 and 50 are interpreted as drawn to methods comprising administering multispecific targeting proteins comprising at least one first binding site which binds to a CEA target site on a tumor, and at least one second binding site which specifically binds to an epitope on an enzyme, carboxylesterase; optionally, administering a clearing agent to clear the targeting protein; administering an enzyme, carboxylesterase; optionally, administering a clearing agent to clear the enzyme; administering a prodrug composition, CPT-11, wherein the enzyme acts on the prodrug to release a therapeutic agent. Claims 51 and 52 are drawn to kits and sterile injectable preparations for targeting a therapeutic agent, comprising multispecific targeting proteins comprising at least one first binding site which binds to a CEA target site on a tumor, and at least one second binding site which specifically binds to an epitope on an enzyme, carboxylesterase; optionally, a clearing agent to clear the targeting protein; an enzyme,

carboxylesterase; optionally, a clearing agent to clear the enzyme; a prodrug composition, CPT-11, wherein the enzyme acts on the prodrug to release a therapeutic agent.

Iwasa teaches a targeting method comprising administering a bispecific antibody that is specific for a target site and specific for an enzyme. Iwasa teaches that methods for making bispecific and trispecific antibodies with desired specificities are known in the art (In the case of Iwasa the target site is a thrombus and the enzyme is streptokinase or urokinase. Iwasa teaches that the enzyme is administered after the bispecific antibody (column 7, lines 19-26), and teaches the advantages of using a bispecific antibody for targeting instead of using a monospecific antibody that is covalently bound to an enzyme (col. 1, line 64-column 2, line 15). Iwasa fails to teach a method where a prodrug is administered and fails to teach antibodies specific for the CEA target site. Either Bosslet, or Blakey provides teachings that demonstrate that the targeting of CEA is well known in the art; and also teaches the general idea of localizing enzymes to a target site for the specific purpose of locally converting a prodrug to its active form. Iwasa, Bosslet, and Blakey fail to teach a prodrug and therapeutic agent combination of CPT-11 and camptothecin where the prodrug is acted upon by a carboxylesterase. However, the teachings of Potter demonstrate that the prodrug CPT-11 is well known in the art and is acted upon by carboxylesterases to produce camptothecin. Potter also teaches that specific carboxylesterases that activate CPT-11 to camptothecin are known and that antibodies may be made to these carboxylesterases. Thus, it would have been prima facie obvious to one of skill in the art to combine the teachings of Iwasa, and any of Bosslet or Blakey, and Potter to make the claimed methods. In view of the teachings of Iwasa concerning some of the drawbacks of using antibody enzyme conjugates, where the conjugates are made by covalent linkage between the antibody

and enzyme, one of ordinary skill in the art would have been motivated to modify the methods of either Bosslet or Blakey. In view of the teachings of Iwasa demonstrating how to make bispecific and trispecific antibodies, one of ordinary skill in the art would have had a reasonable expectation of success in making a bispecific antibody with a specificity for CEA and a carboxylesterase.

12. Claims 1-7, 14, 45, 46, 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iwasa (U.S. Patent 5,506,135, issued April 9, 1996; effective filing date Sep. 26, 1989) in view of either Bosslet et al (Bosslet, K. et al, Cancer Research, 54: 2151-2159, 1994; IDS ref. "A29"), or Blakey et al (Blakey, D.C. et al, Cancer Res. 56: 3287-3292, 1996), and further in view of Potter et al (Potter, P.M., Cancer Research, 58(16): 3627-3632, 1998, August; abstract only), and further in view of King et al (U.S. Patent 5,846,019; issued Jan. 26, 1999; effective filing date Jun. 11, 1991).

Claims 1-7, 14, 45, 46, 49-52 may be interpreted as above but where the targeting protein comprises a fusion protein comprising the first and second binding site (claim 3) or where the targeting protein comprises a covalent conjugate of at least two single chain antibodies, wherein at least one single chain antibody provides the first binding site and at least one single chain antibody provides the second binding site (claim 4). Iwasa fails to teach hybrid or bispecific antibodies that are fusion proteins or conjugates comprising single chain antibodies. However, techniques for making such species of bispecific antibodies are known in the art as evidenced by the teachings of King (see abstract and column 3, line 3 – column 6, line 20). Thus, it would

have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted the bispecific antibodies of King for the bispecific antibodies of Iwasa.

13. Claims 1, 2, 5-7, 14, 36-41, 45, 46, 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iwasa (U.S. Patent 5,506,135, issued April 9, 1996; effective filing date Sep. 26, 1989) in view of either Bosslet et al (Bosslet, K. et al, Cancer Research, 54: 2151-2159, 1994; IDS ref. "A29"), or Blakey et al (Blakey, D.C. et al, Cancer Res. 56: 3287-3292, 1996), and further in view of Potter et al (Potter, P.M., Cancer Research, 58(16): 3627-3632, 1998, August; abstract only), and further in view of Griffiths et al (U.S. Patent 5,965,131; issued Oct. 12, 1999; effective filing date Oct. 9, 1996.)

Claims 1, 2, 5-7, 14, 36-41, 45, 46, 49-52 may be interpreted as reading on methods where the first optional step of administering a clearing agent (step (b) of claim 1) is performed. The clearing agent may be an anti-idiotypic monoclonal antibody, may be modified by sugar residues, and where the modification of the clearing agent is on lysine residues of the clearing agent, at least about 48 percent or at least about 76 percent. The combination of Iwasa, Bosslet, Blakey and Potter fails to teach methods where clearing agents are administered. However, the use of clearing agents, comprising anti-idiotypic antibodies, to improve antibody-targeting methods is known in the art as evidenced by the teachings of Griffiths (see abstract; col. 1, line 61 – column 3, line 51; column 5, line 20 – col. 6, line 30; claims). Griffiths teaches and claims anti-idiotypic antibodies useful as clearing agents where the clearing agents are modified by sugar residues. Thus, it would have been prima facie obvious to one of skill in the art at the time

the invention was made to have modified the methods Iwasa, Bosslet, Blakey and Potter to add clearing agents as taught by Griffiths.

14. Claims 1, 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iwasa (U.S. Patent 5,506,135, issued April 9, 1996; effective filing date Sep. 26, 1989) in view of either Bosslet et al (Bosslet, K. et al, Cancer Research, 54: 2151-2159, 1994; IDS ref. "A29"), or Blakey et al (Blakey, D.C. et al, Cancer Res. 56: 3287-3292, 1996), and further in view of Potter et al (Potter, P.M., Cancer Research, 58(16): 3627-3632, 1998, August; abstract only) in view of Sharma et al (Sharma, S.K. et al., Br. J. Cancer, 61: 659-662, 1990; IDS ref. "A28").

Claims 1, 31 and 32 are drawn to methods where the targeting protein, the enzyme or both is labeled with a detectable label so that before administering the pro-drug, the location of the targeting protein-enzyme conjugate may be detected first. Iwasa, Bosslet, Blakey and Potter do not teach methods where the targeting protein-enzyme conjugate is labeled and detected before administration of the prodrug. However, it would have been prima facie obvious to one of skill in the art at the time the invention was made to have wanted to ascertain if localization to the tumor site had been achieved before administering a prodrug in view of the teachings of Sharma that inefficient clearance of targeting protein results in toxicity when the prodrug is administered (page 659, 1st column) before clearance of targeting protein-enzyme conjugate from the circulation.

15. Claim 53 is rejected under 35 U.S.C. 103(a) as being unpatentable Bosslet et al (Bosslet, K. et al, Cancer Research, 54: 2151-2159, 1994; IDS ref. "A29"), or Blakey et al (Blakey, D.C.

et al, Cancer Res. 56: 3287-3292, 1996), in view of Potter et al (Potter, P.M., Cancer Research, 58(16): 3627-3632, 1998, August; abstract only).

Claim 53 is drawn to a method of administering a targeting protein-enzyme conjugate and interpreted to read on a method where the targeting protein is specific for CEA antigen, the enzyme is a carboxylesterase, and the prodrug is CPT-11. Either of Bosslet or Blakey teaches a targeting protein-enzyme conjugate comprising a targeting protein specific for CEA. Either of Bosslet or Blakey fails to teach a prodrug that is CPT-11 or an enzyme that is carboxylesterase. However, in view of the teachings of Potter, which demonstrate that CPT-11 is a well known prodrug that is converted to its active form by carboxylesterases, it would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the targeting protein-enzyme conjugates of either Bosslet or Blakey with a carboxylesterase of Potter and to use CPT-11 as the prodrug.

Conclusion

No claim is allowed. This rejection is not final in view of the new art rejections.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
July 30, 2001

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